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**METABOLISM IN HYPERTHYROIDISM AND  
HYPOTHYROIDISM\***

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A comprehensive review of the field of metabolism in diseases of the thyroid gland is obviously an impossible task in the brief space at our disposal, nor would it serve the purpose for which these gatherings are designed. During the past two decades the interest of the physiologists and physicians in the subject has resulted in numerous investigations which have brought forth now well established facts of great value to the practitioner. The purpose of this talk is to consider some of the practical problems in the diagnosis and management of diseases of the thyroid in so far as alterations in metabolism are concerned.

By far the most common diseases of the thyroid are believed to be due to either diminished or increased activity of the gland, in its elaboration and discharge into the general circulation of the hormone thyroglobulin. Of the thyroid insufficiencies, myxedema in adults and cretinism in children are easily recognized clinically. The diffuse symmetrical enlargements of the thyroid gland at puberty and in the low iodine areas are associated with a slight insufficiency. All conditions in which there is over-activity are usually designated as hyperthyroidism, "toxic thyroids" or exophthalmic goiter. Fortunately malignant disease of the thyroid is much less common as is also acute and chronic thyroiditis.

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## BASAL METABOLISM

The level of the basal metabolism is now recognized by both physiologists and clinicians as one of the best indications of the activity of the thyroid gland. As early as 1893 Friedrich Müller called attention to the emaciation and loss of weight in spite of the high caloric intake in exophthalmic goiter patients which suggested to him that the total metabolism was increased in this disease. By 1897 Magnus-Levy had demonstrated an increased oxygen consumption in hyperthyroidism, and diminished oxygen consumption in cretinism and myxedema. It was not until 1912 that the work at the Russell Sage Institute of Pathology and Carnegie Nutrition Laboratory provided us with an apparatus and method for the determination of basal metabolism which was suitable for clinical purposes. Since then the apparatus has been simplified and improved so that at the present time basal metabolism determinations have become a part of the routine in all well organized clinics and many doctors' offices. As a test of thyroid activity basal metabolism determinations have proved of great value in diagnosis and treatment of the diseases of the thyroid gland. There are, however, certain limitations of a laboratory test of this type. The technic, while not particularly difficult, is full of pitfalls which may lead to errors amounting to 10 or even 20 per cent. The normal standards in general use are for most purposes adequate, but it should be remembered that an occasional normal individual may have a basal metabolism well outside the range set as normal for the test. The diet and state of nutrition are important. In the under nourished the metabolism is lower while in the well nourished it may be elevated. The state of mind, the trained versus the untrained subject, the muscular tone are all factors necessary of consideration in slight or moderate variations from the normal mean. While there may be a tendency for errors in different directions to neutralize one another there is always a possibility of a combination tending to a large discrepancy in a single instance. In certain diseases

there are well recognized variations from normal. A slightly elevated metabolism is frequently found in hypertension, malignancy, pregnancy, acromegaly, leukemias, polycythemia and infections. On the other hand, a lowered basal metabolism may be present in the anemias, Addison's disease, many skin diseases, tumors of the pituitary gland and in diabetes.

#### THYROID INSUFFICIENCIES

The physician receives little help in identifying myxedema or cretinism from basal metabolism determinations. The clinical picture is characteristic and unmistakable. The B.M.R. is usually 30 per cent or more below the normal average. A B.M.R. of —40 per cent is considered to indicate a total lack of thyroid activity although as low as —59 per cent has been reported. Supplying the needed hormone by the administration of one of the several thyroid preparations can be successfully and safely carried out if reasonable care be exercised. A certain comfort, however, is derived from following the effect of treatment with basal metabolic rates. Inconsistencies between the clinical picture and the B.M.R. do occur as the following case will illustrate. An unmarried woman of 35 presented a classical picture of myxedema. Repeated B.M.R. determinations were within normal limits, the lowest value being —11 per cent. Subsequent experience revealed the fact that with six grains daily of the Burroughs Wellcome preparation all signs and symptoms of myxedema disappeared although the B.M.R. never went above +6 per cent, except on one occasion when the patient on her own account increased the daily intake to eight grains. After two weeks she developed outspoken symptoms of hyperthyroidism, nervousness, sweating, and a rapid pulse. Her basal at this time was +19 per cent.

Situations more confusing and difficult are those met in patients with a low B.M.R. without the clinical features of myxedema. Some of these patients unquestionably have a diminished thyroid activity and are markedly improved

following the administration of thyroid substance sufficient to bring their B.M.R. to within the normal range. Others either have a low B.M.R. normally or are suffering from disturbances other than within the thyroid gland. The administration of thyroid gland as a therapeutic test is probably the best method of differentiating these cases. In addition to the effect on the clinical condition the B.M.R. control is of great advantage. Thyroid gland should be given in amounts sufficient to bring the B.M.R. to within normal limits. Occasionally the result is spectacular and improvement is striking. In other cases without any change in the B.M.R. the patient may complain of accentuation of existing symptoms and no clinical benefit result. Still others with large doses of thyroid extract no beneficial change is observed in the clinical picture nor is there the expected rise in B.M.R. Carefully controlled administration of thyroxin by mouth or parenterally may be tried. The low B.M.R. in our experience is encountered most frequently among those patients who complain of nervousness, easy fatigueability, sensitivity to cold and menstrual disorders. They are usually individuals who are worried over their ability to maintain a satisfactory social or economic position in the community; lack force of character; have a low blood pressure; and are poor physical specimens. As a rule their B.M.R. is seldom lower than —20 per cent and it is in this group that thyroid gland therapy is most disappointing. A small percentage of patients apparently exhibit what seems to be a true hypothyroidism, the B.M.R. is usually as low as —25 per cent or lower and they improve with thyroid gland administration.

The adolescent goiter is associated probably with slight insufficiency. Frequently the girls have a B.M.R. between —15 and —20 per cent. The normal variation of the B.M.R. among youths of the adolescent age is greater than among adults, frequently on the low side. Most of the individuals with adolescent goiter living outside the endemic goiter areas probably need little treatment. It is our practice, however, following the advice of Marine, to administer

small doses of thyroid substance (Burroughs Wellcome Co.) gr. ii daily for two weeks, and, after two weeks' rest, iodine in the form of syrup of hydriodic acid, 30 minims daily for two weeks. This regime is carried out three or four times a year. If no change in the size of the gland occurs within a year or at least two years there is little likelihood such measures will result in any change. In our experience of several years at the Presbyterian Hospital it must be said that only an occasional instance of significant reduction in the size of the gland has been observed. This apparently is contrary to the experience of physicians practicing in the endemic areas where iodine administration is usually followed by a reduction in the size of the gland. A few patients of this type have come to us who have been given sufficient thyroid extract to produce a true exophthalmic goiter, a therapeutic procedure which cannot be too strongly condemned.

#### HYPERTHYROIDISM

As in thyroid deficiency the B.M.R. aids the clinician but little in the diagnosis of clear cut cases of hyperthyroidism. The test is of service in following the course of treatment be it medical or surgical. There is a temptation on the part of physicians to lean too heavily on this test. The wise clinician will place equal importance upon the course of the disease clinically. It is perhaps most useful in judging the optimum effect of iodine administration in preparation for operation and following the effect of radiotherapy.

Occasionally patients are seen where there appears to be wide discrepancies between the basal metabolism and the clinical impression. In one patient A. L. (258530) a housewife of 57 entered the dispensary June 3, 1930, with the sole complaint of constipation. The physical examination revealed little except an elevated blood pressure 210/110 and a secondary anemia (Hgb. 58, RBC 3,200,000). After six months' observation with liberal doses of iron ammonium citrate the blood improved (Hgb. 78, RBC 4,400,000) but little progress was made with relief of

constipation. The B.M.R. at this time was +38 per cent without any discoverable signs or symptoms of hyperthyroidism. Two months later the B.M.R. was +59 per cent. After iodine administration the B.M.R. fell to —5 and —1 per cent with relief of constipation and a general betterment in sense of well being. In this case it may reasonably be assumed we were dealing with hyperthyroidism which would have escaped without the aid of the B.M.R.

As opposed to the above case is A. K. (378839) a woman of 34 admitted to the clinic May 18, 1933, complaining of nervousness following a stillbirth three years ago with a marked increase in symptoms during the past year and a loss of 27 pounds. Clinically there seemed to be no question of the diagnosis of hyperthyroidism. There was a distinct stare without exophthalmos, edema of the eyelids, a moderate symmetrical enlargement of the thyroid gland, an over-acting heart with a rate of 96, and a fine tremor of the fingers. Contrary to expectations the B.M.R. was only +14 per cent. Because of the mild grade of the symptoms, the slight enlargement of the thyroid gland and undoubtedly influenced by the low B.M.R. it was decided to try radiotherapy. Treatments were given three weeks apart. After the third treatment the B.M.R. was +32 per cent, and after the fifth +51 per cent, although clinically she has shown steady improvement. She is still under treatment and we anticipate the B.M.R. will fall.

Another patient illustrates the lack of parallelism between the B.M.R. and clinical impression. O.F. (264282) a colored domestic, age 43, widow, came under our observation July 24, 1930, with unmistakable hyperthyroidism clinically supported by the B.M.R. which was +55 per cent. Her B.M.R. determinations are reported in detail.

Date	B. M. R.	Pulse	Remarks
July 24, 1930	+55	80	Seen in O. P. D. Operation delayed at patient's request.
August 19, 1930	+50	84	Admitted to hospital August 17. Sodium iodide 0.1 gm. daily started.

August	26, 1930	+51	100	Sod. iodide increased to 0.2 daily.
September	3, 1930	+94	108	Good clinical improvement. Sod.
September	4, 1930	+84	92	iodide discontinued. Lugol's 2 mils daily.
September	9, 1930	+40	108	Partial thyroidectomy September 10, 1930.
September	18, 1930	+22	100	Made an excellent convalescence from operation.
September	22, 1930	+26	80	Discharged from hospital.
February	27, 1931			Gained weight and doing housework. Not nervous, no palpitation or tremor.
August	21, 1931	+65	76	No evidence of hyperthyroidism.
November	21, 1931	+68	88	No symptoms of hyperthyroidism.
August	19, 1932	+46	72	No discoverable enlargement of remnant of thyroid gland.
August	4, 1933	+40	68	Continued in excellent condition.

Were it not for the consistency of the several B.M.R. determinations, the accuracy of the observation might be challenged. There is a striking lack of correspondence between the B.M.R. and clinical condition. This case further illustrates the occasional lack of correlation between the pulse rate and B.M.R.

#### HEART DISEASE

Since the introduction of basal metabolism determinations into clinical use a real advance has been made in bringing to light cases of hyperthyroidism masquerading as heart disease. The test has served to improve the keenness of the clinical eye. Many of the patients in this category have few or no discoverable signs of hyperthyroidism and appear to be suffering solely from heart disease. The patient is usually over forty, frequently fibrillating, with unmistakable evidence of cardiac failure. There is no exophthalmos, no enlargement of the thyroid gland, no nervousness, profuse perspiration or tremor yet the B.M.R. may be markedly elevated. Attention may be drawn to these cases by the poor response to digitalization. Following partial thyroidectomy the clinical improvement leaves no doubt as to the correctness of the diagnosis.

Furthermore the pathological laboratory demonstrates a hyperactive gland on microscopic examination. As an illustration of this condition the following case is reported. L.B. (358799), 47, single woman, in domestic service entered the hospital October 20, 1932, complaining of dyspnea, palpitation, nervousness and insomnia. Her palms were not moist, there was no exophthalmos; the thyroid gland was moderately enlarged; the heart was enlarged with unmistakable signs of mitral stenosis, the rate was rapid and totally irregular. The diagnosis was rheumatic heart disease, mitral stenosis and fibrillation, with a debatable element of hyperthyroidism since she had an enlarged thyroid and a B.M.R. of +25 per cent. Several weeks of rest with digitalis resulted in no marked improvement. A partial thyroidectomy was performed following which the cardiac situation improved rapidly. Six months after operation there were no cardiac symptoms although she was still fibrillating without pulse deficit.

Another case—L.C. (367468), a Chinaman of 57 entered the hospital January 1, 1933, complaining of swollen legs, palpitation, dyspnea and cough with occasionally blood streaked sputum of three months' duration. He was an apathetic individual distinctly icteric, not suggesting hyperthyroidism in the least. The thyroid gland was slightly enlarged and possibly a slight stare noted in the eyes but no exophthalmos. His heart was large, without organic valvular disease, rate rapid and regular: His liver enlarged and tender: Edema of the lower legs. He was considered to be a case of arteriosclerotic heart disease. On rest and digitalis for several weeks no significant improvement was made. A basal metabolism determination was made and found to be +52 per cent. Partial thyroidectomy was followed by slow but distinct improvement, the jaundice cleared and signs of cardiac decompensation disappeared. He left for China April 10.

The extraordinary benefit derived from partial thyroidectomy in patients similar to these just described has led Blumgart and Levine to reduce the level of metabolism in



individuals with chronic heart disease but without hyperthyroidism by total ablation of the thyroid gland. Several cases are reported and the results give much promise. The period of observation has been too short to permit any definite statement concerning the advisability of so revolutionary a procedure.

One of the difficult problems with which the physician is frequently confronted is the differential diagnosis between psychoneurosis and hyperthyroidism. In many psychoneurotics the clinical picture is suggestive of hyperthyroidism. There may be a B.M.R. of +15 to +20 per cent. Each patient presents a particular situation and I know of no scheme by which a separation can be made with certainty. Without doubt many individuals have lost part of their thyroid gland unnecessarily and probably others have missed the opportunity of relief by operation. A large number of patients assigned to the group of psychoneurotics have normal B.M.R. so that any marked increase in basal should be viewed with suspicion. When doubt exists the patient with moderately increased basal should be closely observed in good circumstances, with rest and sedatives and frequent B.M.R.s made to determine its persistence. In certain of these cases the effect of iodine on the basal is of considerable diagnostic aid. If the B.M.R. be lowered following the administration of iodine then iodine should be discontinued to determine whether the basal is to return to its original level. A repetition of the experiment is desirable. A drop in the B.M.R. with clinical improvement following iodine administration is certainly suggestive of hyperthyroidism. On the other hand when no reduction of the basal is observed in such a procedure we consider the evidence in favor of the absence of hyperthyroidism.

#### MALIGNANT DISEASE AND THYROIDITIS

The basal metabolic rate is of little aid in the diagnosis of malignant disease of the thyroid. Of twenty-four cases reviewed at the Presbyterian Hospital there were B.M.R.

determined on twelve. In eight cases the basal was within normal limits, the remaining —17 and —23 per cent, +39 and +80 per cent. The same may be said of acute and chronic thyroiditis. All of the basals in the few cases we have observed, eight in all, have been within normal limits.

#### GENERAL METABOLIC CONSIDERATIONS

The effect of hyperthyroidism or hypothyroidism on the protein, carbohydrate and fat metabolism can be explained largely, if not wholly, on the basis of the increased or decreased level of heat production. With adequate fat and carbohydrate, protein minima correspond to those found in normals. There appears to be no difficulty in the utilization of carbohydrate on the part of the hyperthyroid and the inability to store it is due to the increased demand for food. It has been observed that the cholesterol in the blood is increased in hypothyroidism and decreased in hyperthyroidism. This fact is considered by Hurxthal of value as a differential diagnostic aid in puzzling cases but I have had no personal experience with it.

The enormous increase in heat production in hyperthyroidism means that an increased amount of food is needed for the patient. We hear the "high caloric diet" mentioned frequently in connection with the treatment of hyperthyroidism either surgically or medically. Many times the so-called high caloric diet as prescribed is inadequate. Numerous observations now confirm the fact that these patients require much more than the normal 10 or 20 per cent increase over basal requirements at rest. As much as 75 or 100 per cent increase over their basals may be necessary to maintain nitrogen equilibrium and bring about a gain in weight in the hyperthyroid patient. From a practical standpoint gain in weight answers the question whether the patient is receiving sufficient food. We have found the B.M.R. a useful guide in securing adequate food intake. It is usually possible by employing concentrated foods to get the patients to take twice as many calories as the B.M.R. calls for.

The role of iodine in the physiology of the thyroid is a fascinating topic but only a few practical phases of the subject can be mentioned. The place this element holds in the prevention of non-toxic hyperplasia of the thyroid gland and its value in preparation of toxic cases for operation is well established. The extent to which iodine reduces the B.M.R. is usually in direct proportion to the initial elevation. In 185 unselected cases we have studied at the Presbyterian Hospital the average drop in the basal after iodine administration when the level was between +20 and +30 per cent was 9 per cent; with an initial basal between +70 and +80 per cent the average drop amounts to between 35 and 40 per cent. The above observation served as a standard with which to compare the effect of diiodotyrosine which has been so enthusiastically recommended in the recent German literature as superior to the inorganic preparation in common use. Chemically diiodotyrosine would seem to be the precursor of thyroxin, moreover almost all of the organic iodine in the thyroid gland is in the form of either thyroxin or diiodotyrosine. On the hypothetical basis that these two organic iodine compounds normally are in equilibrium in the gland, hyperthyroidism might result when thyroxin is present in excess, hypothyroidism when diiodotyrosine predominates. Our chemical studies of normal and pathological glands have failed to bring support to such a hypothesis. The claims made for the therapeutic use of diiodotyrosine is that it reduces experimental hyperthyroidism, known to be unaffected by inorganic iodine compounds; that it is effective in so-called iodine refractory cases; and that iodine escape is less frequent. In a study of thirty cases including three patients who had previously received iodine, we could detect no difference in the effect of diiodotyrosine and that observed with Lugol's solution and sodium iodide. The reducing effect on the basals was commensurate in both preparations, nor was any change produced by diiodotyrosine in the iodine refractory patients. Our clinical experience with diiodotyrosine appears to be consistent with observations made in the laboratory. When rabbits are given gram

doses of diiodotyrosine about 10 per cent is excreted as inorganic iodine, the rest either unchanged or as a lactic acid derivative. When given in the therapeutic amounts of 100 milligram doses to patients a larger percentage may be broken down to give inorganic iodine.

A word of warning against the indiscriminate use of iodine may be ventured. We have already mentioned its use in the adolescent goiter and as a therapeutic aid in selected cases. Long continued use of iodine in patients with nodular glands occasionally transforms a non-toxic gland to a toxic gland. I know of no advantage to be gained in administering iodine to individuals with non-toxic nodular glands. The great value of iodine in bringing about remissions in the toxic glands, either diffuse or nodular, in preparation for operation must always be considered when one contemplates the use of iodine therapeutically in toxic cases. The temporary effect of iodine makes it essential to reserve iodine for pre-operative use. It is true that cases are reported, and I have seen such, demonstrating a control of the toxicity over long periods until spontaneous recovery occurs, but in my experience iodine has proved disappointing in the medical management of toxic goiter. The impression that once the iodine effect is obtained and the patient "escaped", little benefit may be expected in the subsequent use of iodine is not correct. After a period, one to four weeks, without iodine even though it has been administered over a several months' period we note satisfactory responses. It must be said, however, that the second trial often results in a less striking response.

#### CONCLUSION

I have endeavored to point out in the foregoing remarks how a knowledge of the deviations from normal of the metabolism in hyper- and hypo-thyroidism may be of service to the clinician. One impression I hope to make. Laboratory tests of function are valuable aids when given their proper place and importance. They have increased

our knowledge of disease and have contributed to our clinical ability. It must be remembered, however, that they often represent single components of a complicated system of dependent variables. The danger not only in diseases of the thyroid, but in Medicine generally, is to become a slave to laboratory data and place too little reliance on good clinical judgment.

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